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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,358	02/05/2004	William Stern	P/546-279 REISSUE	8408

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 05/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,358	STERN, WILLIAM	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/21/06 has been entered.

Receipt is acknowledged of the Amendments and Remarks filed on 03/21/06. Accordingly claims 13-44 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-18, 20-21, 24-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In claims 13, 24, 41 and 42 the new range of 10-25mM is considered new matter because the specification does not have

support for the said range. The Provisional Application of 60/180,241 also has no support for the said range.

Claims 13-18, 20-21, 24-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In claims 15, 31 and 43-44 the range for osmotic pressure of from 250 to 350 mOsm/liter is considered new matter since the specification does not provide support for the said range. This range was disclosed in the claims of the parent U.S. Patent 6,440,392, but has no support in the Provisional Application of 60/180,241.

Claims 13-18, 20-21, 24-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The term "the aggregate concentration of all such bioavailability..." is considered new matter. There is no support for the said term in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Grebow et al (5,026,825).

Grebow et al teaches an intranasal formulations comprising calcitonin and excipients. The salmon and chicken calcitonins have a potency of about 4,000 to 6,000 MCR U/mg peptide (col. 3, lines 4-15). The said formulations may be administered across the **nasal membranes** as a spray, nose drop or aerosol (col. 11, lines 15-21).

Grebow also discloses that the nasal spray solutions are especially preferred with water or in a buffer at a **pH of between 3.0 and 8.0** using a buffer system including a mixture of sodium citrate and citric acid in the range of **0.01 M to 0.5 M**. This concentration was found effective to **provide stability** of the dissolved calcitonin in the diluent base or vehicle (col. 11, lines 35-47). Furthermore the formulations are said to have been made in 0.2M buffer at a pH value of 4.1 (col. 14, lines 34-35). The preparations may also comprise other additives including stabilizers, tonicity adjusters, viscosity builders, preservatives and the like (col. 11, lines 48-52). The said additives include methyl paraben, propyl paraben, phenethyl alcohol, etc. Grebow discloses certain suitable concentration ranges of the said additives in the table of column 12.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim13-14, 17, 20-23, 34 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grebow et al (5,026,825).

Although Grebow, discussed above, does not anticipate the formulations comprising clacitonin and citric acid and a citric acid salt, where the pH is from 3.5 to 3.9, it broadly discloses a pH range of 3.0 to 8.0 and selecting a pH range within the disclosed pH range would have been obvious to one of ordinary skill in the art. In other words optimization of ranges or in this case, variation of pH values are obvious to one of ordinary skill in the art and support for patentability.

Claim 13-14, 16-23, 34 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kagatani et al (5,026,825).

Kagatani et al teach compositions for intranasal administration comprising calcitonin at least one absorption enhancer and liquid carriers and diluents suitable for application to the nasal mucosa (col. 1, lines 50-65). The clacitonins can be salmon calcitonin, human calcitonin, porcine calcitonin, etc (see paragraph bridging cols. 1 and 2). The agents used to enhance absorption of calcitonin include benzyl alcohol, Macrogol 400, ethanol, etc (col. 2, lines 3-13). The pernasal medical composition may

be in the form of an aqueous solution. A buffer solution including citrates in a preferred **pH range of 3 to 5** is employed. The examples show formulations having a **pH of 4.0**, The formulations may also contain **polyoxyethylene sorbitan monooleate** (col. 2, lines 16-49). kagatani does not disclose a specific amount for surface active agents, however, it is considered that it would be at least 0.1%

Kagatani also discloses that the aqueous solution for nasal administration comprises from 200 to 6000IU/ml of calcitonin (see col. 3, lines 5-10). Examples 1 and 4-6 show various ingredients such as salmon calcitonin, citric acid, sodium citrate, benzyl alcohol, etc, and their concentration ranges for the said formulations.

Although Kagatani does not anticipate the formulations comprising clacitonin and citric acid and a citric acid salt, where the pH is from 3.5 to 3.9, it teaches formulations having a pH range of form 3.0 to 5.0, with examples indicating a pH of 4.0. It is considered that selecting a pH range within the disclosed pH range would have been obvious to one of ordinary skill in the art. In other words optimization of ranges or in this case, variation of pH values are obvious to one of ordinary skill in the art and support for patentability.

Claims 15, 24-28, 30-33, 35-39 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grebow et al (5,026,825) in view of Dua et al (The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits).

Grebow et al, discussed above, lacks disclosure on specific tonicity and viscosity of the intranasal formulations of calcitonin.

Dua et al compare the effect of different tonicity and viscosity levels of the formulation on absorption of the calcitonin from the nasal mucosa. Dua discloses studies performed with a formulation at a viscosity of about 1 and a formulation at a **viscosity of about 76 cp**. Dua also discloses that suitable tonicity for intranasal formulations of calcitonin is from **100 to 600 mOsm** and a **pH of about 4.0** was accomplished using buffers (see abstract and page 235, col. 1, lines 7-11). Dua concludes that the droplet size distribution produced by the metered nasal spray pump at 1 cps viscosity was gaussian and unimodal (see page 239, column 1, lines 45-47).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the intranasal formulations of calcitonin as disclosed by Grebow et al to include the viscosity and tonicity limitations of the intranasal formulations of calcitonin as disclosed by Dua et al with the reasonable expectations of successfully preparing efficient and stable formulations with suitable and recognized viscosity and tonicity for nasal administration.

Claims 14-15, 24-33, 35-39 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kagatani et al (4,788,221) in view of Dua et al (The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits).

Kagatani et al, discussed above, lacks disclosure on specific tonicity and viscosity of the intranasal formulations of calcitonin.

Dua et al compare the effect of different tonicity and viscosity levels of the formulation on absorption of the calcitonin from the nasal mucosa. Dua discloses studies performed with a formulation at a viscosity of about 1 and a formulation at a **viscosity of about 76 cp**. Dua also discloses that suitable tonicity for intranasal formulations of calcitonin is from **100 to 600 mOsm** and a **pH of about 4.0** was accomplished using buffers (see abstract and page 235, col. 1, lines 7-11). Dua concludes that the droplet size distribution produced by the metered nasal spray pump at 1 cps viscosity was gaussian and unimodal (see page 239, column 1, lines 45-47).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the intranasal formulations of calcitonin as disclosed by Kagatani et al to include the viscosity and tonicity limitations of the intranasal formulations of calcitonin as disclosed by Dua et al with the reasonable expectations of successfully preparing efficient and stable formulations with suitable and recognized viscosity and tonicity for nasal administration.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chiodini et al (5,719,122) teaches compositions comprising calcitonin in dosage forms including intranasal administration. The formulations comprise a mixture of citric acid and sodium citrate as buffers and other ingredients.

Response to Arguments

Applicant's arguments with respect to claims 13-44 filed on 03/21/06 have been considered but are moot in view of the new ground(s) of rejection.

Applicant argues that claims 22 and 23 "represent a classic example of a new use of an old compound—citric acid". Applicant believes that prior art does not teach the use of citric acid in such formulations to enhance stability or bioavailability. This is not persuasive because stability and bioavailability are **inherent properties** of the formulations. Furthermore Grebow states that adding the said range of citrate concentration to the formulations was found effective to **provide stability** of the dissolved calcitonin in the diluent base or vehicle (col. 11, lines 35-47). Thus it is clearly shown that this finding was not a discovery of the Applicant.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mina Haghighatian
May 10, 2006

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